*Bulletin of the World Health Organization*, 63 (5): 899 – 904 (1985) 

# Case-control study to identify risk factors for paediatric endemic typhoid fever in Santiago, Chile

ROBERT E. BLACK,[1] LUIS CISNEROS,[2] MYRON M. LEVINE,[3] ANTONIO BANFI,[4] HERNAN LOBOS,[5] & HECTOR RODRIGUEZ [6]

*Typhoid fever is an important endemic health problem in Santiago, Chile. Its incidence has more than doubled in recent years, during which access to potable water and sewage disposal in the home became almost universal in the city. A matched case-control study was carried out to identify risk factors and vehicles of transmission of paediatric typhoid fever; 81 children in the 3–14-years age group with typhoid fever were compared with controls, matched with respect to age, sex, and neighbourhood. It was found that case children more frequently bought lunch at school and shared food with classmates. Also, case children more often consumed flavoured ices bought outside the home; none of 41 other food items considered in the study was associated with a higher risk of typhoid fever. Only two food handlers for cases and one for controls were positive for* Salmonella typhi, *indicating that persons preparing food solely for their own family were not the main source of* S. typhi *infection. Rather, the risk factors identified in this study are consistent with the hypothesis that paediatric endemic typhoid fever in Santiago is largely spread by consumption of foodstuffs that are prepared outside the individual's home and are shared with or sold to children.*

Typhoid fever is an endemic health problem in Chile, presenting some interesting and mostly unexplained epidemiological features. The illness has a marked seasonality with a peak during the summer months and the highest incidence is in children in the 8–13-years age group (*1*, *2*). Furthermore, its incidence is high in children from both low and high socioeconomic groups, even those who live under apparently nearly optimum sanitary conditions (*3*).

Significant improvement has been achieved in reducing the mortality rate of typhoid fever in Chile from 12 per 10 000 inhabitants in the 1940s to less than 1 per 10 000 in the late 1970s; however, over the same period the morbidity rate has increased from 50 per 10 000 inhabitants to 100 per 10 000 (*4*). Paradoxically, this increase in morbidity occurred during a period in which access to potable water and sewage disposal in the home increased and became almost universal in urban areas (*3*, *5*). Furthermore, during this time there was a striking reduction in the frequency of most other communicable diseases in Chile (*6*).

Little is known about the routes of transmission for typhoid fever in Santiago. The two principal hypotheses proposed suggest contamination of food (*a*) by foodhandlers who are asymptomatic carriers of *Salmonella typhi* (*2*) or (*b*) by the irrigation of fruit and vegetables with sewage-contaminated water (*7*, *8*). As far as the first hypothesis is concerned it should be noted that the prevalence of cholelithiasis in Chile is one of the highest in the world (*9*) and that this, together with the endemic presence of typhoid fever in the country (*1–4*), produces a high rate of chronic biliary carriage. It has been estimated that there are nearly 30 000 such carriers of *S. typhi* in Santiago (a prevalence rate of 694 per 10 000 (*10*)). With regard to the second hypothesis, sewage in Santiago is discharged untreated into the Mapocho river and a large canal; water drawn from these sources is used to irrigate crops, such as lettuce and celery, which are grown near the city (*7*). High faecal

[1] Chief, Epidemiology Section, Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD 21201, USA (to whom requests for reprints should be addressed).

[2] Fellow, Center for Vaccine Development.

[3] Director, Center for Vaccine Development.

[4] Chief, Infectious Diseases Unit, Calvo MacKenna Children's Hospital, Santiago, Chile.

[5] Scientific Director, Institute of Public Health, Santiago, Chile.

[6] Epidemiology Consultant, Ministry of Public Health, Santiago, Chile.

coliform counts have been measured in this water, and *S. typhi* organisms have been isolated from it (*8*).

The aim of the present study was to identify risk factors and vehicles of transmission of typhoid fever in the eastern part of Santiago, an area that accommodates families of all economic strata, but mostly middle- and high-income persons living in modern housing.

## MATERIALS AND METHODS

A matched case-control study was conducted from December 1980 to June 1981. Cases selected were children of either sex in the age group 3–14 years who lived in the eastern area of Santiago and who were diagnosed as having typhoid fever as confirmed by blood and/or bone marrow cultures that were positive for *S. typhi*. Children were diagnosed and treated at the Calvo McKenna Hospital (serving mainly low and middle socioeconomic groups) or by 20 paediatricians who care more for middle and upper socioeconomic groups in their private practices. A surveillance system was established to ensure that two blood cultures were obtained from each child with suspected typhoid fever at either the hospital or the private practices. Blood was cultured in a medium of supplemented peptone broth,[a] and processed by standard methods (*11*, *12*).

Controls were children of the same sex and age (± one year of age) as the cases, and lived in the same neighbourhood. They were identified by following a standardized route which started at the home of the case. Controls who had had a febrile illness suggestive of typhoid fever during the four weeks prior to their participation in the study were excluded and a new control was selected. Once an appropriate control was identified, return visits to the neighbourhood were made until complete information was obtained.

Two public health nurses filled in questionnaires concerning cases and their matched controls, and the answers given by the children were verified by interviewing their mothers. For young children, the questions were answered by their mothers. Cases and matched controls were interviewed by the same nurse. The questionnaire explored the following areas: socioeconomic level (type of house construction and ownership; number of rooms, beds, and persons in house; and ownership of car); sanitary conditions at home (existence of a water source and bathroom facilities); food and drink consumption (42 items), both at home and outside (for the two weeks prior to the onset of illness in cases and over the same period for the matched controls); existence of cooks and/or maids at home and their role in food preparation; frequency of eating food from street vendors, in restaurants, or at school; history of gall bladder disease among the food handlers at home; contact with known cases of typhoid fever (in the two months preceding the study); and travel and swimming activities (in the month prior to onset of illness for cases and in the same period for the matched control).

For both cases and controls two stool samples were obtained from the primary food handler in the household. The initial sample was obtained by rectal swab at the time of the interview and placed in Cary-Blair transport medium and cultured the same day. The second sample was a stool obtained during the morning of the following day which was kept refrigerated and was cultured within six hours. Faecal samples were cultured on *Salmonella-Shigella*, MacConkey's, or bismuth sulfite agars, either directly or after selenite enrichment for 24 hours; colonies harbouring *Salmonella* or *Shigella* bacteria were identified using standard techniques (*12*).

Statistical analysis of the results for matched pairs was carried out using the McNemar test (*13*) if the outcome was dichotomous, and a similar test derived by Fleiss (*13*) if trichotomous.

## RESULTS

Eighty-one cases met the criteria for inclusion in the study; 67 were from Calvo McKenna Hospital and 14 were from the practices of private paediatricians in Santiago. The largest number of cases were 6-year olds, with relatively few below this age and fairly uniform frequencies above it; there were equal numbers of male and female children (Fig. 1).

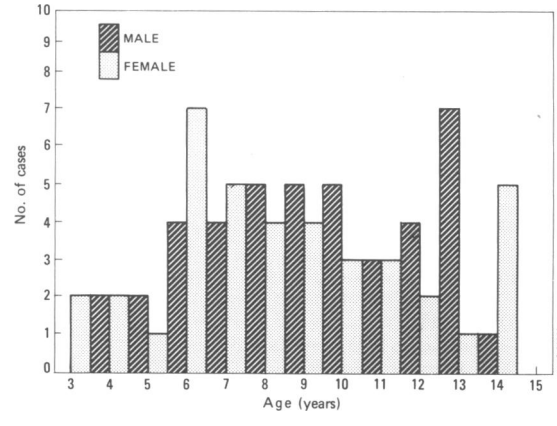


Fig. 1. Age and sex distribution of 81 paediatric cases of typhoid fever in the eastern area of Santiago, Chile, over the period December 1980–June 1981

[a] From Becton Dickinson and Co., Oxnard, CA 93030, USA.

Table 1. Association of selected risk factors with paediatric typhoid fever in Santiago, Chile

| | Case:Control pairs | | | | | |
|---|---|---|---|---|---|---|
| | Yes:Yes | Yes:No | No:Yes | No:No | Significance | Relative risk |
| History of typhoid fever in a relative | 0 | 16 | 5 | 58 | $\chi^2=4.8$, $P<0.05$ | 3.2 |
| Bought lunch at school[a] | 2 | 12 | 3 | 35 | $\chi^2=4.3$, $P<0.05$ | 4.0 |
| Travel outside Santiago | 12 | 8 | 21 | 40 | $\chi^2=5.0$, $P<0.05$ | 0.4 |
| Swimming in a lake | 9 | 0 | 8 | 72 | $\chi^2=6.1$, $P<0.025$ | 0 |
| Swimming in a pool | 10 | 7 | 18 | 46 | $\chi^2=4.0$, $P<0.05$ | 0.4 |

[a] Analysis confined to cases that occurred while school was in session.

Rectal swabs were obtained from 78, and stool samples from 77, of the 81 domestic food handlers for cases; 2 food handlers were positive for *S. typhi*, including the mother of one case and the cook (female) of another. Swabs were also obtained from 81, and stools from 71 food handlers of controls. One of these food handlers was positive for *S. typhi*; this was the mother of a control child whose own children were negative for *S. typhi* but who prepared flavoured ices that she sold to neighbourhood children, including the case matched with her child. The ages of these food handlers were 34, 37 and 55 years; none of them had a history of typhoid fever, but two had a history of biliary colic and one was known to have gallstones. Seven additional food handlers had stool cultures positive for other enteropathogens, including *S. paratyphi* B (3), other salmonellae (3) and *Shigella* (1).

The families of cases and matched controls had the same number of persons in the home, and all had household electricity, sewage disposal facilities, sinks in bathroom and kitchen, and a source of water, or owned a refrigerator or an automobile. The relatives of cases (usually cousins), but not friends, were more frequently (relative risk 3.2) reported ill with typhoid fever during the two months preceding the study (Table 1). Cases more frequently (relative risk 4.0) ate lunch bought at school than controls (Table 1), but both groups ate food from street vendors, school kiosks, and restaurants. In addition, cases more frequently shared food at school with friends (Table 2). This increased risk was particularly apparent for children who shared food in this way three or more times per week (relative risk 6.0) (Table 2), and seemed to be more important for children who brought food to school (relative risk 10/2, $\chi^2=5.4$, $P<0.05$) than for children who purchased school food (relative risk 2/0, not significant).

Controls travelled away from Santiago more frequently than did cases in the month before the onset of illness in the matched case (Table 1). This lower risk for controls who travelled seemed to hold during both summer (relative risk 5/10) and non-summer (relative risk 3/10) months. Controls also swam more frequently in a lake or pool than cases (Table 1).

The consumption patterns of cases for 42 fruits and vegetables and other food products were obtained for two weeks prior to onset of their illness and for the same period in matched controls. Consumption of

Table 2. Frequency of sharing food with friends among typhoid fever cases and matched controls[a]

| | No. of matched controls sharing food | | |
|---|---|---|---|
| No. of cases sharing food | ⩾3 times/week | 1-2 times/week | Never |
| ⩾3 times/week (12)[b] | 0 | 9 | 3 |
| 1-2 times/week (29) | 2 | 15 | 12 |
| Never (34) | 0 | 11 | 23 |

[a] $\chi^2=7.3$, $P<0.05$ (2 degrees of freedom).

[b] Figures in parentheses are totals.

Table 3. Frequency of consuming purchased flavoured ices by typhoid fever cases and matched controls[a]

| Case consumption | Control consumption | | |
|---|---|---|---|
| | ⩾3 times/week | 1-2 times/week | Never |
| ⩾3 times/week (36)[b] | 15 | 8 | 13 |
| 1-2 times/week (11) | 4 | 5 | 2 |
| Never (34) | 3 | 5 | 26 |

[a] $\chi^2 = 7.3$, $P < 0.05$ (2 degrees of freedom).

[b] Figures in parentheses are totals.

purchased flavoured ices was associated with a higher risk of typhoid fever, particularly among children consuming such ices three or more times per week (relative risk 3.0) (Table 3). Consumption of flavoured ices made in the home was not associated with typhoid fever (relative risk 5/9). No association was found between consumption of the other food items, including suspected vehicles or groups of these items, and development of typhoid fever. For example, the relative risk associated with consumption of lettuce was 14/19 (0.74) and strawberries 23/19 (1.2). One food item, *mote con huesillos* (a local drink made from corn and apricots), was associated with a significantly lower risk of typhoid fever (relative risk 4/16, $\chi^2 = 9.9$, $P < 0.01$).

## DISCUSSION

The epidemiology of endemic diseases is frequently complex. Unlike common-source outbreaks, many vehicles, each responsible for a few cases, may be involved, and this might be the situation regarding typhoid fever in Santiago, Chile. The present study incriminated only one food item but identified a number of factors associated with a higher or lower risk of developing typhoid fever.

Since more than 70 variables were investigated, it can be expected that a few of them are statistically significant by chance alone at a $P$ level of less than 0.05. In some instances, however, the statistical significance of the association was greater than 0.05. Furthermore, some risk factors were corroborated by statistical significance of two or more related variables, e.g., travel outside Santiago and swimming in lakes or pools, usually outside the city. Since these are related variables, the finding of all three to be important factors suggests that this was not due to chance. Cases were probably matched so closely with controls from the same neighbourhood for socioeconomic status that potential risk factors associated with wealth, education, or place of residence may have been overlooked. On the other hand, this study design allowed examination of important risk factors without the potentially confounding effects that may have arisen had cases and controls differed in socioeconomic status.

The study identified flavoured ices as a vehicle of transmission of typhoid fever among children in Santiago; however, the precise means of contamination of the ices has not yet been established. One possibility is that the water used to prepare them was contaminated, but the almost universal household access to water of good quality in study families and in Santiago in general (*5*) and the failure of this study to implicate the water source as an important risk factor suggest that this is unlikely. Another possible explanation is that *S. typhi* carriers contaminated the containers, the water, or the ice in their homes while preparing the flavoured ices for sale. In this respect, it is pertinent that we identified an *S. typhi* carrier who had prepared and sold flavoured ices to a child who subsequently developed typhoid fever. The lack of significance, as a risk factor, of flavoured ices made and consumed at home further emphasizes that it is the preparation of the food item by carriers outside the home that is important.

Consuming lunch bought at school cafeterias and sharing food with classmates who did not buy lunch at school were both associated with a higher risk of typhoid fever. Although we did not detect any clustering of cases in particular schools, these data suggest that one transmission route of *S. typhi* may be consumption at school of food that was prepared on the school premises, brought by their children from home, or bought from food vendors. It is also possible that certain children have a tendency to eat food prepared outside their own homes, thus exposing themselves to food prepared by a wide variety of persons, some of whom could be chronic carriers of *S. typhi*. The higher frequency of reported (but undocumented) typhoid fever among relatives of cases compared to those of controls could be due to reporting bias; however, it may indicate that the case and the relative had shared a common food exposure.

The reduced risk of typhoid fever among children who travelled out of Santiago may be a marker of socioeconomic status but could also indicate that they were removed from the source of infection, being safer away from the city. The incidence rates of typhoid fever in the popular holiday resorts are much lower than those in Santiago (*2*).

This study indicates that food handlers who prepared food solely for their own families were not

the main source of *S. typhi* infection. Cultures of two stool samples should identify most asymptomatic carriers, and only two carriers were found in the homes of the 81 cases. Furthermore, this finding was corroborated by a later study of family members of typhoid fever patients in Santiago (*15*). Using three stool cultures and measurement of Vi antibodies (*16*), only one chronic carrier was found among the family members of 24 patients with typhoid fever. Although chronic carriers are undoubtedly important in the transmission of *S. typhi*, all these studies indicate that such carriers within the household could account for only a small fraction of typhoid fever cases. The risk factors identified in the present study are consistent with the hypothesis that endemic typhoid fever in Santiago is largely spread by exposure to food items that are prepared in schools, private homes, or by food vendors and that are shared with or sold to children. From this study, it cannot be determined whether contamination of these items with *S. typhi* was a result of their preparation by chronic *S. typhi* carriers or because the raw foodstuffs were contaminated by *S. typhi* from Santiago sewage. Further epidemiological and bacteriological studies are planned to resolve this issue.

## ACKNOWLEDGEMENTS

This study was funded by grants from the World Health Organization, the Pan American Health Organization, and by research contract No. DAMD 17-C-1115 from the US Army Medical Research and Development Command. The authors would like to thank the paediatricians of the eastern area of Santiago who helped in identifying cases of typhoid fever, Margarita Canales and Viviana Sotomayor for field data collection, Aurora Maldonaldo for laboratory assistance, and Dr Catterine Ferreccio for helpful comments on the manuscript.

## RÉSUMÉ

ETUDE CAS-TÉMOINS EN VUE DE DÉTERMINER LES FACTEURS DE RISQUE DE LA FIÈVRE TYPHOÏDE ENDÉMIQUE DE L'ENFANT À SANTIAGO DU CHILI.

La fièvre typhoïde est un problème de santé endémique au Chili, qui atteint un paroxysme pendant l'été et sévit surtout chez les enfants de 8 à 13 ans. A Santiago, l'incidence de la fièvre typhoïde a doublé ces dernières années, bien que la quasi-totalité des ménages aient accès à l'eau potable et à l'évacuation des eaux usées; l'incidence est élevée, tant dans les quartiers pauvres que dans les quartiers riches de la ville. Une étude de cas et de témoins appariés a été entreprise en vue de déterminer les facteurs de risque et les véhicules de transmission de la maladie. Quatre-vingt un enfants de trois à quatorze ans, souffrant de fièvre typhoïde confirmée par analyse bactériologique ont été comparés à des sujets témoins appariés par âge, sexe et voisinage. L'étude a révélé des facteurs de risque qui correspondent à l'hypothèse selon laquelle, à Santiago, la consommation de produits alimentaires partagés par les enfants ou vendus à ceux-ci hors de la maison est dans une large mesure responsable de la propagation de la maladie. La contamination de ces produits par *Salmonella typhi* peut être due à leur préparation par des porteurs chroniques de *S. typhi* ou au fait que les denrées entrant dans leur composition contiennent *S. typhi* par suite d'une pollution par les eaux usées.

## REFERENCES

1. FERRECCIO, C. ET AL. Benign bacteremia caused by *Salmonella typhi* and *paratyphi* in children younger than 2 years. *Journal of paediatrics*, **104**: 899-901 (1984).
2. MEDINA, E. & YRARRAZAVAL, M. [Typhoid fever in Chile: epidemiological considerations.] *Revista de medicina de Chile*, **111**: 609-615 (1983) (in Spanish).
3. BORGONO, J. M. & LATORRE, M. [Current situation concerning the epidemiology of typhoid fever in the province of Santiago.] *Revista de Chile de higiene et medida preventiva*, **15**: 53-64 (1964) (in Spanish).
4. RISTORI, C. [Epidemiology of typhoid fever in Chile.] *Boletín de vigilancia epidemiología de Ministerio de Salud, Chile*, **8** (1-2): 3-5 (1981) (in Spanish).

5. URRUTIA, J. M. [Evaluation and study of the quality of potable water in Chile during the period 1971–76.] *Problemas de Salud y Medio Ambiente. Recapitulación temática Ministerio de Salud-Chile, Departmento de Programas sobre Ambiente, 1978*, Santiago, Chile (in Spanish).
6. BORGONO, J. M. & COREY, G. 25 years of an integrated vaccination programme in Chile. *Developments in biological standardization*, **41**: 301–306 (1978).
7 BESOAIN, R. M. [Irrigation with contaminated water in metropolitan regions of Chile: perspective solutions to the public health problem.] *XV Convención Upadi: Medio Anmbiente y su Impacto Socio-Económico*. Santiago 1978, pp. 327–349 (in Spanish).
8. SEARS, S. D. ET AL. The use of Moore swabs for isolation of *Salmonella typhi* from irrigation water in Saniago, Chile. *Journal of infectious diseases*, **149**: 640–642 (1984).
9. BRETT, M. & BARKER, D. J. P. The world distribution of gallstones. *International journal of epidemiology*, **5**: 335–341 (1976).
10. LEVINE, M. M. ET AL. Precise estimation of the numbers of chronic carriers of *Salmonella typhi* in Santiago, Chile, an endemic area. *Journal of infectious diseases*, **146**: 724–726 (1982).
11. GILMAN, R. ET AL. The relative efficacy of blood, urine, rectal swab, and rose spot cultures for recovery of *S. typhi* in typhoid fever. *Lancet*, **1**: 1211–1213 (1975).
12. KELLY, M. T. ET AL. Enterobacteriaceae. In: *Manual of clinical microbiology*, Washington, DC, American Society for Microbiology, 1985, pp. 263–277.
13. FLEISS, J. The analysis of data from matched samples. In: *Statistical methods for rates and proportions*, New York, J. Wiley and Sons, 1981, pp. 112–137.
14. FEEMSTER, R. F. & SMITH, H. M. Laboratory criteria of the cure of typhoid carriers. *Americal journal of public health*, **35**: 368–372 (1945).
15. MORRIS, J. G. ET AL. Typhoid fever in Santiago, Chile: a study of household contacts of paediatric patients. *American journal of tropical medicine and hygiene*, **33**: 1198–1202 (1984).
16. LANATA, C. F. ET AL. Vi serology in detection of chronic *Salmonella typhi* carriers in an endemic area. *Lancet*, **2**: 441–443 (1983).